REMARKS

Applicant recognizes with appreciation that Examiner indicates that Claims 10 and 13 have been allowed.

In this Amendment, Applicant has amended Claims 14 – 15 to specify different embodiments of the present invention and overcome the rejection, and added new Claims 33 – 34. It is respectfully submitted that no new matter has been introduced by the amended claims. All claims are now present for examination and favorable reconsideration is respectfully requested in view of the preceding amendments and the following comments.

REJECTIONS UNDER 35 U.S.C. § 112 FIRST PARAPGRAPH:

Claim 15 has been rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

It is respectfully submitted that the rejection is incorrect. Please note that the present Claim 15 is directed to a composition comprising 13-HODE in its free form and a pharmaceutically acceptable carrier. The Examiner indicated that Claim 15 was rejected because the specification does not provide sufficient written description to support the (A)/(B)/(C) combination (Office Action, page 5, lines 8 – 10). However, as recognized by the Examiner, Claim 15 is not directed to the (A)/(B)/(C) combination (Office Action, page 3, lines 11 – 12). In addition, the Examiner admitted that the instant specification discloses a composition comprising 13-HODE in its free form or with a pharmaceutically acceptable carrier (Office Action, page 3, lines 13 – 14). Furthermore, the Examiner recognizes that "the specification provides sufficient written description for the composition comprising (A) 13-HODE ... and (C) carrier ..." (Office Action, page 4, lines 1 – 7 from bottom). Because there is adequate written description in the

specification with regard to the embodiments defined in Claim 15, the rejection of Claim 15 based on inadequate written description is incorrect.

Therefore, the rejection under 35 U.S.C. § 112, first paragraph has been overcome. Accordingly, withdrawal of the rejections under 35 U.S.C. § 112, first paragraph, is respectfully requested.

REJECTIONS UNDER 35 U.S.C. § 102:

Claims 15 – 17 have been rejected under 35 U.S.C. § 102 (b) as allegedly being anticipated by Streber (US 5,102,912), hereinafter Streber.

Applicant traverses the rejection and respectfully submits that the present-claimed invention is not anticipated by the cited reference. More specifically, Streber fails to disclose, explicitly or inherently, all the limitations of Claims 15 – 17. In addition, Claim 15 has been amended to further specify that "for use in reducing the inhibition of endogenous 13-HODE synthesis in a subject." Claims 16 – 17 also include this feature due to their dependency on Claim 15.

At first, Streber does not explicitly disclose the combination of 13-HODE, in an amount equal or less than 100 mg, with a pharmaceutical carrier, such as a mono-, di- or triglyceride oil. As admitted by the Examiner in the previous Office Action of August 26, 2002, "[T]he teaching of Streber differs from the claimed invention in the corporation of phospholipids (lecithin) in 13-HODE formulation." (page 7, lines 4 – 5). The Examiner further admitted that "specific examples of 13-HODE formulation is not disclosed in Streber" (Office Action of April 23, 2003, page 8, lines 6 – 7).

In addition, Streber does not inherently disclose the combination of 13-HODE, in an amount equal or less than 100 mg, with a pharmaceutical carrier, such as a mono-, di- or triglyceride oil. "To establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency,

however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.' " *In re Robertson*, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999). The Examiner has not provided evidence showing that the claimed combination is necessarily present in the disclosure of Streber.

As previously stated, the Examiner oversimplified the problems of administering fatty acids and does not appreciate the many specific differences if each type of phospholipids, fatty acids and other lipids. Each specific lipid has its own specific properties which depend on its precise chemical composition and which are not necessarily possessed by other specific lipids. Applicant submits that Streber relates to diseases produced by oestrogen and to other situations. Streber does not describe oral formulation but of 9-HODE and not 13-HODE which is quite different substance with quite different properties.

Therefore, the embodiments of the present invention as claimed are different from Streber, and they have components and effects which are not disclosed nor taught in Streber. In summary, the newly presented claims are not anticipated by Streber and the rejection under 35 U.S.C. § 102 (b) has been overcome. Accordingly, withdrawal of the rejections under 35 U.S.C. § 102 (b) is respectfully requested.

REJECTIONS UNDER 35 U.S.C. §103:

Claims 14 – 17 and 19 – 23 have been rejected under 35 U.S.C. §103 as allegedly being unpatentable over by Vanderhoek et al. (US 6,077,525), hereinafter Vanderhoek, in view of Breivik et al. (US 5,502,077), hereinafter Breivik. Claim 18 has been rejected under 35 U.S.C. §103 as allegedly being unpatentable over Streber in view of Carlsson et al. (WO 99/44585), hereinafter Carlsson.

Applicant traverses the rejection and respectfully submits that the embodiments of present-claimed invention are not obvious over Vanderhoek in view of Breivik. At first, Claims 14 and 15 have been amended to further specify that "for use in reducing the

inhibition of endogenous 13-HODE synthesis in a subject." Claims 16 – 23 also include this feature due to their dependency on Claims 14 – 15.

It is respectfully submitted that a person of ordinary skill in the field of thrombosis, vascular disease and its treatment would recognize that the underlying etiology is multi-factorial, involving hypercoagulability, platelet activation, inflammation and vascular dysfunction. This same person would know that all of these are exacerbated by specifically known risk factors, including smoking, hyperlipidermia, hypertension, and diabetes, (Mehta *et al.*, J. Am. Coll. Cardiol. 31: 1217, 1998; Karp *et al.*, Am. J. Epid. 160: 707, 2004; Satter *et al.*, Circ., Oct. 18, 2004; Yusuf *et al.*, Lancet 364: 937, 2004). Moreover, such a person would recognize that simply lowering cholesterol, decreasing hypertension, impairing platelet function or treating diabetes alone **will not** prevent vascular disease (Ascaso *et al.*, Am. J. Cardiovasc. Drugs 4: 299, 2004; Yusuf, Am. Heart J. 148:52, 2004; Morimoto *et al.*, Am. J. Med. 117: 459, 2004; Briel *et al.*, Am. J. Med. 117: 596, 2004). In addition, most current treatments, particularly anti-platelet agents and anti-coagulants place patients have the risk of bleeding and hemorrhagic stroke.

Therefore, (cardio)vascular disease is a multi-factorial entity that requires a combination of drug treatments to attenuate its progression. From the perspective of anti-platelet agents such as aspirin and GPIIbIIIa inhibitors, which have been shown to attenuate acute and short-term myocardial infarctions and thrombotic stroke (Aspirin Trialists Collaboration, Br. Med. J. 308: 159, 1994; The EPILOG Investigators, N Engl. J. Med. 336: 1689, 1997). These agents do not prevent vascular wall hyperplasia, (re)stenosis or alter vascular wall biocompatibility. In fact, there is no currently used antithrombotic agent that prevents vascular wall hyperplasia, (re)stenosis or alters vascular wall compatibility.

Vanderhoek provides a single example of a highly complex formulation of 9, 11 octadecadienoic in combination with many different ingredients including monoglyceride (see Example 3). However, 9, 11 octadecadienoic is a different compound from 13-HODE. Moreover, Figure 3 of Vanderhoek teaches away from the use of 13-HODE as

an inhibitor of platelet aggregating TXB_2 formation compared to 13-HODE. Therefore, Vanderhoek does not disclose the combination of 13-HODE in a simple mixture with either a glyceride or an ethyl ester nor does it suggest that such formulations would be useful for treating cardiovascular and related disease. By reading EP 0 955 047, the skilled artisan would not be led to formulations containing 13-HODE with a glyceride or an ethyl ester.

The Examiner states that Vanderhoek and Breivik teach the use of conjugated fatty acids including ethyl-EPA, 13-HODE, and antioxidants for inhibiting platelet aggregation and it would be obvious to a person of ordinary skill in the relevant art to configure some combination thereof to optimize vascular wall biocompatibility. Applicant respectfully disagrees with the Examiner and submits that the current invention is not obvious over Vanderhoek in view of Breivik. More specifically, a person of ordinary skill in the art would know that omega-3 fatty acids that prevent platelet aggregation *in vitro* or *ex vivo* provide **no clinical benefit** to patients with (cardio)vascular disease (The EMPAR Study, Cairns et al. Circ. 94: 1553, 1996). These investigators demonstrated in clinical trials that conjugated dietary fatty acids thought to attenuate platelet function have **no effect** on the reduction of coronary (re)stenosis in patients undergoing percutaneous transluminal coronary angioplasty. Other investigators have reported that increased levels of 13-HODE are associated with **increased atherogenesis** (Feinmark & Cornicelli, Biochem. Pharmacol. 54: 953, 1997; Ylä-Herttuala et al., Proc Natl Acad Sci USA 87: 6959, 1990; Ylä-Herttuala et al., J. Clin. Invest: 95: 2692, 1995). Therefore, a person of ordinary skill in the art would be faced with the conundrum that the literature indicates that anti-platelet agents *per se* have no benefit on vascular biocompatibility, and 13-HODE, in particular, appears to have detrimental effects. Thus, the prior art teaches away from the use of instantly claimed compositions as having both an "anti-platelet effect" and "a vascular effect".

Finally, a person skilled in the art would realized that all prior art antithrombotic treatments, including those taught by Vanderhoek and Breivik, impact significantly on coagulation and/or platelet function and render platelets hemostatically dysfunctional; i.e., place the patient at risk of bleeding. The present invention focuses on vascular wall

biocompatibility; i.e., returning the vessel wall to hemeostatis conditions **without rendering the patient hemostatically dysfunctional.** Therefore, the embodiments of the present invention as claimed are different from the disclosures in Vanderhoek and Breivik.

Therefore, the rejection under 35 U.S.C. §103 has been overcome. Accordingly, withdrawal of the rejections under 35 U.S.C. §103 is respectfully requested.

Having overcome all outstanding grounds of rejection, the application is now in condition for allowance, and prompt action toward that end is respectfully solicited.

Respectfully submitted,

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